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THE SYNTHESIS OF 2-AZASTEROIDS

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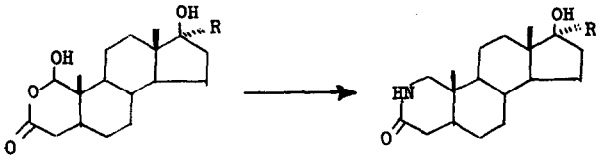
Previous investigations on the synthesis and biological evaluation of 2-oxasteroids have produced compounds possessing desirable anabolic, androgenic, and lipid-lowering properties.[1] As an extension of this work aimed at studying the effect on biological activity of a hetero-atom at the 2-position of steroids we have also prepared several series of 2-azasteroids.[2]

The preparation of saturated 2-azasteroids proved to be straightforward. Condensation of 17β-hydroxy-1-oxo-1,2-seco-androstan-2-oic acid (1a) or its 17α-methyl derivative (1b)[1a,1d] with ammonia in the presence of hydrogen and Raney nickel[3] led respectively to 2-aza-17β-hydroxy-5α-androstan-3-one (2a), mp 265-270°; $\lambda_{max}^{CHCl_3}$ 2.94 and 6.03μ, or its 17α-methyl derivative (2b), mp 305-307°; $\lambda_{max}^{CHCl_3}$ 2.94 and 6.03μ, respectively.



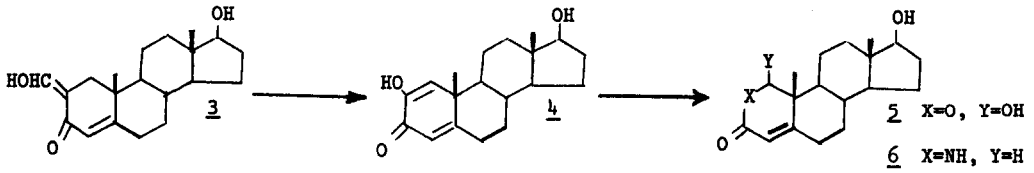
1a R=H
1b R=CH_3

2a R=H
2b R=CH_3

The synthesis of the Δ^4-analogs proved to be more difficult since the Raney nickel-ammonia method was likely to eliminate unsaturation during the reductive amination. Fortunately, it was found that this conversion could be successfully carried out on unsaturated lactols with generation of the desired lactam, using ammonium formate and formic acid with no apparent reduction of the conjugated double bond[4]. This discovery turned out to be the key to the present work.

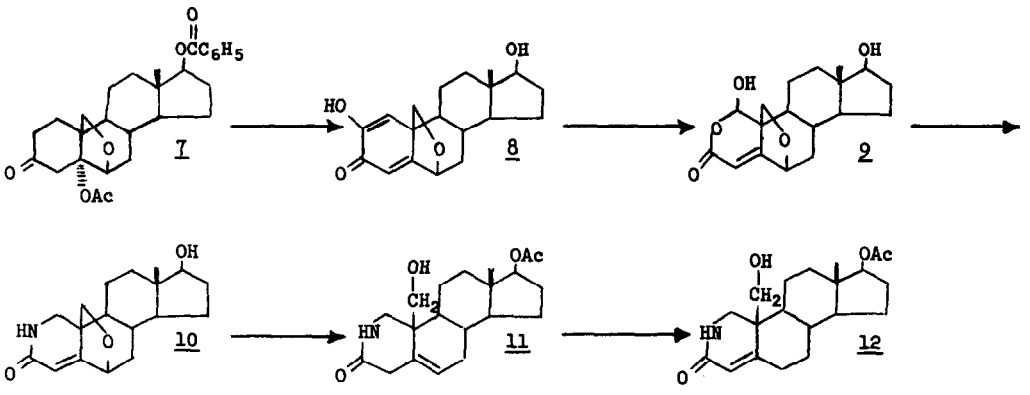
Thus, the lactol which had been previously prepared in poor yield[1a,1d] was synthesized by an alternate improved method. Ozonolysis of 2-hydroxymethylenetestosterone (3) in the presence of dimethyl sulfide in methylene chloride/pyridine afforded 2,17β-dihydroxyandrosta-1,4-dien-3-one (4)[5] in 65% yield. Reaction of this material with oxygen[6] in the presence of cupric ion in

dimethylformamide[7] yielded the lactol 5 in moderate yield (ca. 40%), mp 244-245°; $\lambda_{max}^{CHCl_3}$ 5.80μ; λ_{max}^{MeOH} 226nm (13,900). Leuckart treatment of this material produced 2-azatestosterone (6), mp 280-282°; $\lambda_{max}^{CHCl_3}$ 2.92, 5.95, and 6.15μ; λ^{MeOH} 220nm (12,000); $\delta_{ppm}^{(CDCl_3 + CF_3CO_2D)}$ 0.80 (3H,s,18-CH_3), 1.18 (3H,s,19-CH_3), 3.30 (2H,brd s,1-CH_2), 5.70 (1H,brd s,4-CH), in about 70% yield after basic hydrolysis of the partially esterfied 17-hydroxyl group.

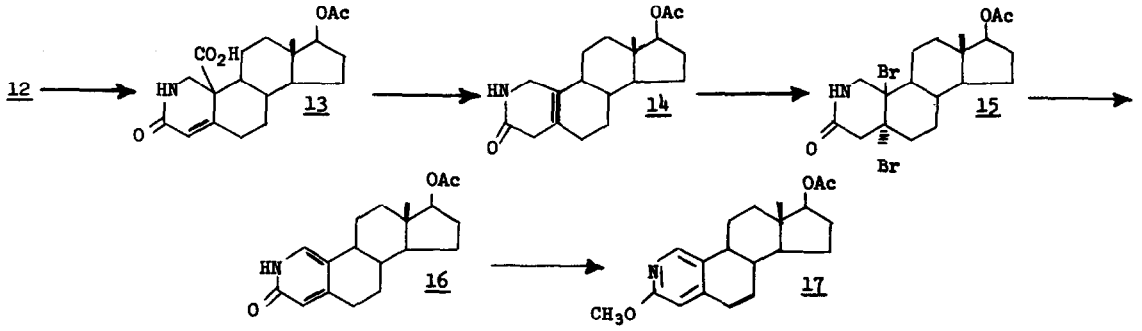


Since removal of the 19-methyl group has been associated with an increase in hormonal properties, it was of interest to prepare 19-nor-2-azasteroids. Utilizing the readily available bridged keto diester 7[8], oxygenation[6] in the presence of potassium t-butoxide[9] afforded after hydrolysis in yields up to 70% 6β,19-oxido-2,17-dihydroxy-androsta-1,4-diene-3-one (8)[12], mp 199-201°; $\lambda_{max}^{CHCl_3}$ 6.03 and 6.12μ; λ_{max}^{MeOH} 253nm (11,600); $\delta_{ppm}^{CDCl_3}$ 0.88 (3H,s,18-CH_3), 3.93 (2H,dd,J=8 Hz, 19-CH_2), 4.77 (1H,d,J=4 Hz,6-CH), 6.23 (1H,s,vinylic-H), 6.27 (1H,s,vinylic-H). Treatment of (8) with ozone at -65° in ethyl acetate, followed by rearrangement of the intermediate molozonide with concomittant loss of carbon dioxide merely upon warming, gave the desired lactol 9 in 60% yield, mp 143-150°; λ_{max}^{KBr} 5.80μ (brd); λ_{max}^{MeOH} 226nm (8,800); $\delta_{ppm}^{C_5D_5N}$ 0.98 (3H,s,18-CH_3), 4.25 (2H,dd,J=8 Hz,19-CH_2), 5.00 (1H,brd d,6-CH), 6.14 (1H,s,4-CH), 6.42 (1H,brd s,1-CH), a key intermediate in the synthesis of the desired 19-nor-2-azasteroids.

When the cyclized acid-aldehyde 9 was refluxed overnight with ammonium formate in formic acid the unsaturated lactam 10 was obtained (50% yield), mp 247-250°; $\lambda_{max}^{CHCl_3}$ 2.93, 5.90, and 6.03μ; λ^{MeOH} 220nm (11,200), after saponification of the partially formylated 17-hydroxyl group. Acetylation followed by reductive cleavage of the 6-ether bridge with zinc-copper couple led to the 19-hydroxy-Δ^5-lactam 11, mp 271-273°; $\lambda_{max}^{CHCl_3}$ 2.93, 5.79, 6.02, and 7.90μ;$\delta_{ppm}^{(CDCl_3 + CF_3CO_2D)}$ 0.87 (3H,s,18-CH_3), 2.15 (3H,s,17-OAc), 3.89 (2H,brd s,19-CH_2), 5.85 (1H,brd m,4-CH), in yields up to 90%. Isomerization to the conjugated lactam 12 was affected by refluxing 11 in piperidine with acetic acid (3:1), mp 265-275°;λ^{MeOH} 220nm (13,200); $\delta_{ppm}^{(CDCl_3 + CF_3CO_2D)}$ 0.87 (3H,s,18-CH_3), 2.13 (3H,s,17-OAc), 3.65 (2H,dd,J=14 Hz,1-CH_2), 4.04 (2H,brd s,19-CH_2), 5.95 (1H,brd s,4-CH).

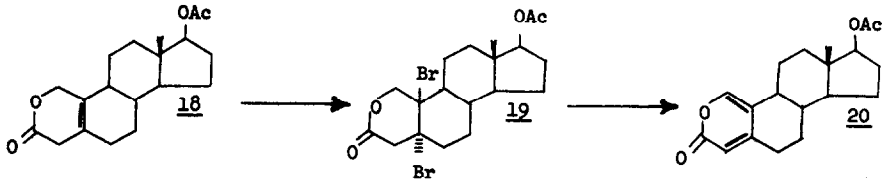


The conversion of 12 to 19-nor steroids was accomplished by the methods described in the 2-oxa series [1c,1d]. Chromic acid oxidation of the alcohol gave the 10-carboxy derivative 13 which was not purified but rather decarboxylated in pyridine-acetic acid (5:1) affording the $\Delta^{5(10)}$-lactam 14, mp > 325°; $\lambda_{max}^{CHCl_3}$ 2.93, 5.79, 6.00, and 7.90μ; $\delta_{ppm}^{(CDCl_3 + CF_3CO_2D)}$ 0.83 (3H,s,18-CH_3), 2.07 (3H,s,17-OAc), 2.90 (2H,brd m,4-CH_2), 3.95 (2H,brd m,1-CH), in ca. 60% yield from 12. Bromination in $CHCl_3$ gave the 5,10-dibromo compound in excellent yield which dehydrobrominated with N-methylpiperidine to produce the unique A-ring pyridone steroid 16 (exclusive of any cross conjugated $\Delta^{4,9(10)}$-diene), mp > 330°; $\lambda_{max}^{CHCl_3}$ 2.93, 5.78, 6.01, 6.16, and 7.90μ; λ_{max}^{MeOH} 306 (5,500) and 231 (7,900); $\delta_{ppm}^{(CF_3CO_2D)}$ 1.02 (3H,s,18-CH_3), 2.27 (3H,s,17-OAc), 7.13 (1H,brd m,4-CH), 8.00 (1H,brd m,1-CH). The α-pyridone 16 was then alkylated with methyl iodide and silver carbonate in benzene[10] to give the interesting 2-azaestradiol-3-methyl ether 17-acetate (17), mp 102-104°; $\lambda_{max}^{CHCl_3}$ 5.80, 6.22, 6.70, 7.30, and 7.90μ; λ_{max}^{MeOH} 277nm (3,730) and 287nm sh; $\delta_{ppm}^{CDCl_3}$ 0.83 (3H,s,18-CH_3), 2.05 (3H,s,17-OAc), 3.88 (3H,s,3-OCH_3), 6.44 (1H,brd s,4-CH), and 8.00 (1H,brd s,1-CH).



A similar series of reactions led to 2-azaestrone-3-methyl ether, mp 139-140°; λ_{max}^{MeOH} 276nm (3,850), 286nm sh, which in turn was converted to 17α-ethynyl-2-azaestradiol-3-methyl ether, mp 141-145°; λ_{max}^{MeOH} 277nm (3,700), 287 sh, by standard ethynylation procedures.

An alternate synthesis of 16 was based on earlier work in the 2-oxa series. It was found that bromination of the $\Delta^{5(10)}$-lactone 18[1c,1d] in chloroform produced the dibromo lactone 19 which upon treatment with N-methylpyrrolidine gave the α-pyrone 20, mp 178-182°; $\lambda_{max}^{CHCl_3}$ 5.78μ (brd); λ_{max}^{MeOH} 300nm (5,750), in excellent overall yield.[11] This could also be converted to 16 by condensation with ammonium acetate in acetic acid in moderate yield (50%).



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2. R. Pappo, R. J. Chorvat, and P. A. Prekel, Abstracts Third International Congress of Heterocyclic Chemistry, Sendai, Japan, 1971, p. 74.
3. We wish to acknowledge the assistance of Mr. W. M. Selby in the preparation of 2a and 2b.
4. The reductive ability of formic acid has not generally been associated with the hydrogenation of C-C double bonds [cf. H. W. Gibson, Chem. Reviews, 69, 673 (1969)]. However, saturation of conjugated double bonds by formate has been known to occur in some cases [cf. M. Sekiya and C. Yanaihara, Chem. Pharm. Bull. (Tokyo), 17, 738 (1969), M. Sekiya and K. Suzuki, ibid., 19, 1531, (1971)].
5. Compound was identical to that synthesized by an alternate method in our laboratories, cf. J. Baran, J. Am. Chem. Soc., 80, 1687 (1958).
6. We wish to thank Mr. M. G. Scaros for performing the various oxygenation reactions.
7. V. Van Rheenen Tetrahedron Lett., 985 (1969).
8. Obtained readily from 3β,5α-diacetoxy-6,19-oxido-androstan-17-one by previously described methods; see U.S. patent 3,644,342 (1972).
9. R. Hanna and G. Ourisson, Bull. Soc. Chim., 1945 (1961).
10. G. C. Hopkins, J. P. Jonak, H. J. Minnemeyer and H. Tieckelmann, J. Org. Chem., 32, 4040 (1967).
11. We are indebted to Mrs. P. Prekel for the study of the conversion of 18 to 20.
12. As pointed out by the referee, it was possible in this case to effect oxygenation of the enolate of the corresponding Δ^4-3-ketone since enolization towards the 6-position was blocked.